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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/020,746	02/09/1998	AVI J. ASHKENAZI	P1101P1	3607

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EXAMINER	
KAUFMAN, CLAIRE M	
ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/020,746	Applicant(s) ASHKENAZI, ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8 and 21-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *8* is/are allowed.

6)☒ Claim(s) *21-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The prosecution on this application is reopened in view of the availability of US Patent 6,072,047 relied upon below as prior art.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This claim is drawn to a dimeric molecule comprising a monoclonal antibody linked to a heterologous immunoglobulin. The subject matter of these claims does not appear to be in the claims or specification as filed. While bispecific antibodies and chimeric antibodies are discussed in the specification (p. 51-53), it does not appear that these antibodies encompass or are encompassed by a dimeric molecule having the limitations set forth in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 21-27 and 34-41 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 6,072,047.

US Patent 6,072,047 teaches an Apo-2 polypeptide called TRAIL-R of SEQ ID NO:2. This patent receives benefit of priority to 08/829,536, filed March 28, 1997, for the full-length receptor polypeptide, which is identical to SEQ ID NO:1 of the instant application with the exception that TRAIL-R has a 39 amino acid insert beginning at either position 182 or 185 of SEQ ID NO:2 of the patent, which insert occurs after amino acid 181 or 184, respectively, of SEQ ID NO:1 of the instant application. Also taught are antibodies and conventional methods of making such antibodies that bind the full-length and extracellular domain of TRAIL-R, including monoclonal and hybridomas producing the antibodies (col. 26, line 21, through col. 27, line 4). Additionally, antibodies that bind TRAIL-R, humanized, chimeric, fragments of antibodies that bind TRAIL-R are taught in col. 20, line 25-67. Agonistic antibodies that mimic ligand binding are described as inducing apoptosis of certain cancer cells (col. 21, lines 35-46).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 6,072,047 in view of US Patent 6,455,262, Ghetie et al. (PNAS, 1997, #127 cited by Applicants) and Shopes (J. Immuol., 1992, #248 cited by Applicants).

US Patent 6,072,047 is relied upon for the teachings set forth above. Also taught (col. 20, lines 50-55) is that "... humanized antibodies ... offer the advantage of reduced immunogenicity when the antibodies are administered to humans." US Patent 6,072,047 does not teach a human antibody, homodimeric antibody or a dimeric molecule as defined in claim 28.

US Patent 6,455,262 teaches human antibodies to TGF-β receptors and provides references for methods of making them (col. 35, lines 28-46).

Ghetie et al. teach that antibodies have been made that can signal apoptosis of tumor cells (p. 7509, col. 1, middle). Also fully disclosed are methods of making homodimers comprised of two monoclonal antibodies (mAb, p. 7509, col. 2 second full paragraph, to p. 7510, col. 1, 4th full paragraph). It is taught that when monomeric mAbs were not particularly effective in growth arrest of or cytotoxic activity against tumor cells, the homodimers were highly effective (*e.g.*, p. 7509, col. 2, first full paragraph).

Shopes teaches dimeric molecules comprising synthesized mAbs (*e.g.*, Fig. 1B, and "MATERIALS AND METHODS"). These molecules are bound tail to tail and display enhanced activity over monomers in assays such as complement-mediated cytolysis (Fig. 3). One proposed reason for their higher activity "...relates to the synergistic effect in complement-dependent lysis with two antibodies directed toward distinct epitopes on the same Ag [antigen]...." (p. 2921, col. 2, first full sentence) It is suggested (p. 2921, beginning of third full paragraph) "that the augmented cytolytic activity of a genetically engineered Ig dimer may be useful in immunotherapy where clearance of Ag-bearing cells by mAb is essential."

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce a human Apo-2 receptor monoclonal antibody that bound the extracellular domain of the receptor and induced apoptosis by using the agonistic antibodies of US Patent 6,072,047 in the method taught by US Patent 6, 455,262, because it was widely recognized and well known in the antibody art that human or humanized antibodies have the advantage when used in human immunotherapy of not provoking an unwanted immune response generally associated with administration of antibodies from other species. This advantage was also stated in US Patent 6,072,047. It further would have been obvious to make homodimeric molecules comprised of two Apo-2 receptor agonistic mAbs by the method taught by Ghetie et al. One would have been motivated to have such a homodimer because Ghetie et al. teach that the

homodimer can be more effective as a cytotoxic agent against tumor cells than monomeric mAbs, and US Patent 6,072,047 teaches using the disclosed agonistic antibodies to induce apoptosis in cancer cells. Additionally, it would have been obvious to make a dimeric molecule comprising an Apo-2 receptor agonistic mAb and a heterologous immunoglobulin using the method of Shopes because he showed that dimeric antibody molecules had higher activity than monomeric mAbs, and that it would be desirable to have a dimeric molecule with two antibodies directed to two distinct epiptopes (*i.e.*, a dimeric molecule with two distinct immunoglobulins) because of the synergistic effect the different antibodies could have on cell lysis. Also, the dimeric molecule has the potential advantage in immunotherapy for clearance of antigen-bearing cells.

Conclusion

Claim 8 remains allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Claire M. Kaufman

Patent Examiner, Art Unit 1646

October 17, 2002.

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SUPERVISORY PATENT EXAMINER.
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